Presenter's Name: Abdo, Rober

Additional Author(s): Li S, Zhang Q

Abstract Title: The Spatial Transcriptomic Landscape of Brain Metastases Derived from Non-small Cell Lung Carcinoma

Abstract:

Brain metastasis (BrM) substantially contributes to cancer-related deaths, comprises the majority of central nervous system malignancies, and dominantly arises from non-small cell lung carcinomas (NSCLCs). Although Immune checkpoint blockade (ICB) targeting immunoregulatory pathways shows promising clinical progress in BrM, the fundamental mechanisms underlying ICB resistance remain poorly understood. Nonetheless, cancer-associated fibroblasts (CAFs) constitute a substantial part of a tumor microenvironment, and their role in BrMs remains elusive. Here, we performed spatial-RNA sequencing on (119) surgically resected NSCLCs and BrM specimens from (44) patients and conducted digital pathology characterization. We identified three distinct classes of the tumor brain microenvironment (TBME) based on fibrosis status: (1) highly fibrotic TBME characterized by highly expressing COL3A1 and shifting astrocytes into the reactive state (2) non-fibrotic TBME distinguished by reprogrammed microglia and less astrocytic plasticity; (3) intermediately fibrotic TBME featured by intermingling characteristics between the highly and non-fibrotic TBMEs. Intriguingly, highly fibrotic TBME is associated with polarized macrophages into pro-angiogenic phenotype, whereas non-fibrotic BTME exhibits greater immune checkpoint signaling. These functional differences of TBME are governed by TGF-β signaling. Our classification provides a systemic view of the highly heterogeneous TBME and suggests future avenues for rational, targeted immunotherapies of BrM.

POSTER PRESENTATIONS 3
3D: PATHOGENESIS OF NEUROLOGIC DISEASES

Presenter's Name: Elliott-Benjamin, Akeida

Additional Author(s): Shkrum M, Mao H, Zhang Q

Abstract Title: Fatal craniocerebral and vertebrospinal injuries caused by low and high falls

Abstract:

Introduction: Falls from heights represent a significant cause of death across all age groups. Falls can vary from accidental causes, suicides, and homicide. Blunt force trauma is almost always the likely result of falls from both high (> 10 meters) and low (< 10 meters) heights where craniocerebral and vertebrospinal injuries prove to be most fatal. Current literature copiously covers the intricacies regarding fracture patterns, survival rate, and recovery from falls. However, a gap still remains regarding how fatal falls mirror themselves in the realm of neuropathology. Our study aims to fill this gap by characterising craniocerebral and vertebrospinal injury patterns from high (> 10 meters) and low (<10 meters) heights and correlating them with the levels of height fallen.

Methods: We began with analysing the data from Statistics Canada regarding causes of morbidity and mortality within the country. All cases with causes of death attributed to "fall" from year 2000 to 2020 were retrieved and analysed. A retrospective study was employed where archived neuropathology and autopsy reports, from 2000 to 2020, at London Health Sciences Centre (LHSC) were reviewed. Demographic information and data regarding craniocerebral and vertebrospinal injuries, reported at the time of autopsy and following histological examination, were collected and analysed. A computer simulation will be performed on selected cases.

Results: The Statistics Canada data revealed that deaths due to falls are increasing over the years where males and individuals over the age of 80 are most susceptible. This data also showed that "other [falls] on the same level" and "[falls] on and from stairs and steps" are the most common scenarios in which fatal falls occur. A total of 321 cases, that mentioned "fall" in their report, were identified at LHSC with 63 cases meeting our initial inclusion and exclusion criteria. Preliminary analysis demonstrated that males are more vulnerable to fatal falls. Additionally, falls down stairs and steps are the most common medium involved with fatal falls.

Discussion: This data will serve to provide key insights about the relationship between fatal fall injury patterns and the height fallen, in addition to identifying demographic groups that are most at risk.

Presenter's Name: Gelinas, Kelcie

Additional Author(s): Phillips A, Walsh JC

Abstract Title: Unexpected Findings in Appendectomy Specimens: LHSC Case Review of 1287 Patients.

Abstract:

Introduction: Appendectomies are one of the most commonly performed surgical procedures, usually due to acute appendicitis. Appendiceal tumours may present with similar clinical symptoms to acute appendicitis, and malignancy may be found incidentally at pathological examination. This study analyzed appendectomy specimens at our institution to ascertain the number of appendices with an incidental malignant finding, and to correlate this with patient demographics.

Methods: Appendectomies performed in 2019 and 2020 were reviewed. Data collected included patient age and sex, indication for surgery, gross abnormality, and final diagnosis. Non-parametric tests were used for data analysis.

Results: Cases reviewed = 1287. Forty-four (3.4%) had unexpected findings. Twenty-seven of these (2% of total) were malignant. Mean age of cases with unexpected malignancy was 54 years, mean age with unexpected benign findings was 44 and mean age with no unexpected findings was 33. There was a statistically significant difference between mean age of patients with unexpected findings vs no unexpected findings ($p < 0.001$ Mann-Whitney), and between unexpected malignancy vs no unexpected findings ($p < 0.001$ Kruskal-Wallis). In 25/27 cases with unexpected malignancy, the presumed clinical diagnosis was appendicitis. Unexpected malignancies were found in 1% patients aged 0-19 years; 0 aged 20-29; 2% aged 30-39; 1% aged 40-49; 1% aged 50-59; 7% aged 60-69; 14% aged 70-79; 5% aged 80-89; 0 aged 90-99.

Discussion: Two percent of appendectomies at our centre had unexpected malignancy, including 2 patients under 20. In patients 60+, the rate of unexpected malignancy was 8%. Thirteen of these cases in older adults (87%) had a clinical diagnosis of appendicitis. These findings warrant careful gross examination of all appendectomy specimens, but especially those removed from older adults, as malignancy could be missed by inadequate sampling.

POSTER PRESENTATIONS 3
3D: PATHOGENESIS OF NEUROLOGIC DISEASES

Presenter's Name: Pejhan, Shervin

Additional Author(s): Tran C, Driman D, Hammond R, Ang LC, Zhang Q

Abstract Title: The impact of COVID19 pandemic on Neuropathology service at the London Health Sciences Centre

Abstract:

The COVID-19 pandemic has had significant impact on medical services. Many countries postponed non-emergent procedures to hold up hospital logistics for the unprecedented situation. Surgical backlogs caused by the COVID-19 pandemic have been evaluated by different groups. However, the impact of this pandemic on pathology and specifically neuropathology (NP) services has received limited attention. In this study we reviewed all NP reports of the London Health Sciences Centre from March 2018 (two years before the pandemic declaration) until end of the year 2021. Demographic information of the patients and their pathology types were collected. For tumors, site, histopathology types and WHO grading were analyzed.

During the studied timeline, the total number of NP samples reached to its lowest in April 2020, corresponding to the first Ontario provincial lockdown and showed variations during the studied time. However, unlike most pathology sub-specialties that resumed to their baseline later during the pandemics, Neuropathology specimens witnessed an increased case volume for several months during the examined pandemic years compared to the pre-pandemic time.

Among the different types of NP surgical specimens, muscle biopsy and epilepsy related specimens showed more significant reduction, compared to neoplasm associated specimens. There were more surgeries for higher grade tumors and metastases during first year of pandemic compared to the previous two years. This volume returned to its pre-pandemic baseline in 2021 (post-vaccination). Interestingly, inflammatory conditions showed gradual increase during the studied period of time.
Our results show that the neuropathology service volume reduction due to the COVID-19 pandemic has not been as significant as some other pathology subspecialties. Studying the variations in histopathological diagnoses in pandemic years could be helpful for future planning in both clinical and pathological sectors, especially when the data is strengthened by experiences of other medical centers.

Presenter's Name: Reilly, John

Additional Author(s): van Jaaarsveld R, Cornips MC, Hadders M, Agolini E, Ahimaz P, Anyane-yeboa K, Bellanger S, van Binsbergen E, van den Boogaard MJ, Brischoux-Boucher e, Caylor R, Ciolfi A, Verheij J, Fontana P,, Hopman S, Iascone M, Javier M, Kamsteeg EJ, Kerkhof J, Kido J, Kim HG, Kleefstra T, Lonardo F, Lai A, Lev D, Levy M, Lewis S, Lichty A, Matsumoto N, Maya I, McConkey H, Mégarbané A, Michaud V, Miele E, Niceta M, Novelli A, Onesimo r, Pfundt R, Popp B, Prijoles E, Relator R, Redon S, Rots D,, Rousault K, Said K, Schieving J, Tartaglia M, Tenconi R, Uguen K, Verbeek N, Walsh C, Yosovich K, Yuskatis C, Zampino G, Sadikovic B, Alders M

Abstract Title: Delineation of a KDM2B-related neurodevelopmental disorder and its associated DNA methylation signature

Abstract:

Mutations in genes involved in the epigenetic machinery are an emerging cause for neurodevelopmental disorders (NDDs). Lysine-demethylase 2B (KDM2B) encodes an epigenetic regulator but has not been recognized as an NDD gene to date. Here we present a cohort of 21 individuals with heterozygous –likely- pathogenic variants in KDM2B. These individuals present with developmental delay and/or intellectual disability, autism, AD(H)D, congenital organ anomalies and facial dysmorphism. To establish this cohort, we assessed 24 variants in 33 individuals. We applied methylation arrays on blood-derived DNA samples to establish a KDM2B-specific epigenetic signature characterized by hypermethylation of CpG-dinucleotides. We identify the CxxC-domain as a mutational hotspot and identify a specific episignature for this subgroup. Importantly, we were able to detect the KDM2B-episignature even in the context of a dual diagnosis with the presence of another episignature, demonstrating the robustness of this assay.

POSTER PRESENTATIONS 3
3D: PATHOGENESIS OF NEUROLOGIC DISEASES

Presenter's Name: Smith, Morgan

Additional Author(s): Hammond R, Pejhan S

Abstract Title: Isolated Angiitis of the Vasa Vasorum (IAVV)

Abstract:

Background: Temporal arteritis, also termed giant cell arteritis, is the most common form of vasculitis affecting patients over 50 years of age. A prompt diagnosis and treatment are required to prevent debilitating vision loss or stroke. The typical clinical presentation includes new onset of headaches, scalp tenderness, jaw claudication, and may or may not include other systemic manifestations such as polymyalgia rheumatica. It is also typical for laboratory testing to reveal elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Temporal artery biopsy is the gold standard for diagnosis where the classic histologic picture is characterized by chronic granulomatous inflammation with or without a giant cell component. While the definition of temporal arteritis is well established, other inflammatory changes may be present whose significance remains uncertain, particularly isolated angiitis of the vasa vasorum (AVV) and small vessel vasculitis of the periadventitia (SVV).

Purpose: The existence of AVV and SVV, as well as their relevance to temporal arteritis and associated systemic inflammatory findings is debated in the literature. Furthermore, patients with isolated AVV have not been clearly distinguished from those with SVV, as the definitions are not well established. Corticosteroid treatment often begins before a histologic diagnosis is confirmed, however, these treatments are not without risk, particularly in elderly patients and those with comorbidities. Patients with AVV and SVV typically undergo treatment, making it difficult to assess the importance of these histopathologic findings.

Aims: The present study aims to examine cases at LHSC biopsied on suspicion of temporal arteritis to determine the significance of isolated AVV and its association with the giant cell arteritis disease spectrum. Slides of the biopsy specimens will be reviewed to arrive at a definition for vasa vasorum and scored based on inflammatory findings affecting the temporal artery, vasa vasorum, and periadventitial small vessels. The clinical records will be reviewed for demographic, diagnostic, treatment, and follow-up data to be recorded and compared against histopathological findings.

Presenter's Name: Thayaparan, Lorelei

Additional Author(s): Gannavarapu S, Newman S, Rupar T

Abstract Title: Understanding Innate Immune Function Using Bone Marrow Derived Macrophages Collected From MLD Mice

Abstract:

Introduction: Metachromatic leukodystrophy (MLD) is a lysosomal storage disease caused by arylsulfatase A (ARSA) deficiency resulting in inadequate sulfatide degradation. Disease progression occurs as the accumulation of sulfatide in myelin and cells of internal organs contribute to myelin sheath damage, subsequent motor/cognitive impairment, and a heightened inflammatory response. While previous studies have observed a rise in proinflammatory cytokines in the cerebrospinal fluid of MLD patients, our understanding of the impact on innate immunity is limited. Moving forward, our laboratory will be looking at one of the most significant innate immune functions, phagocytosis, to determine whether or not altered lysosomal function has an impact on host phagocytes.

Methods: We will be collecting bone marrow derived macrophages from WT and MLD mice, and then measuring phagocytosis through the Fc-gamma signaling pathway using E. coli bioparticles as a target (Vybrant Phagocytosis Assay Kit, V-6694). We will collect results in triplicate at 3, 5, 10, 20, and 60 minutes; to stop phagocytosis at these time points, we will use ice cold phosphate buffered saline (PBS) and 4% paraformaldehyde (PFA). The results will then be deciphered in two ways: (i) using a plate reader and plotting the rate of phagocytosis comparing the two cell lines, (ii) staining the cells with F4/80 antibody and DAPI and proceeding with imaging.

Results: A difference in the rate or overall intake of particles between the cells of WT and MLD mice would imply an abnormality in phagocytosis in MLD.

Discussion: Current treatment approaches are primarily based on preventative care and minimizing disease-related symptoms. This research could further our understanding of the pathophysiology of MLD, paving the way for development of targeted therapeutics and/or a newborn screening method.

POSTER PRESENTATIONS 3
3D: PATHOGENESIS OF NEUROLOGIC DISEASES

Presenter's Name: Twible, Carolyn

Additional Author(s): Zhang Q

Abstract Title: Characterizing the hippocampal dentate gyrus involvement in temporal lobe epilepsy

Abstract:

Introduction: Hippocampal sclerosis (HS) is the most common pathology finding for drug-resistant temporal lobe epilepsy (TLE) and is characterized by neuronal loss and gliotic Cornu Ammonis. Nearly 20% of the surgical specimens obtained from drug-resistant TLE surgery patients contain "normal" populations of neurons yet still benefit from their surgical resection, possibly pointing to a neuropathological explanation for the epileptogenic focus present in the resected tissue that is not able to be detected through standard diagnostic practices. Currently, it is not clear if no-HS represents a subtype of HS, precedes the characteristically observed pyramidal neuron loss, or if no-HS is a distinct disease entity from HS. If no-HS represents a distinct disease entity, some degree of difference should be observed in clinical and/or pathological investigations, particularly in regions overlooked during routine clinical examination (e.g. the dentate gyrus; DG).

Objective: We will characterize the morphological and genomic features of the hippocampal DG in TLE patients and investigate the underlying epileptogenic mechanisms.

Methods: In this study, 21 TLE surgical resection cases were examined, including 14 HS and 7 no-HS cases, to investigate morphometry of the DG. Information on histopathological diagnosis and post-operative outcome were included in a clinicopathological correlation database. The digital image analysis software QuPath was used to perform cell detection analysis on the DG. Measures including Delaunay mean and cell density were analyzed. Eighteen TLE, including 10 HS and 8 no-HS, surgical resection cases were selected for gene expression profiling using the NanoString Neuroinflammatory and Glial Profiling panels.

Results: HS patients show a significant increase in granule cell (GC) spacing and decrease in GC density within the DG compared to no-HS patients. Similarly, HS and no-HS patients that were able to achieve seizure freedom post-operatively demonstrated an increase in GC spacing and decrease in GC density in comparison to cases that did not achieve seizure freedom post-operatively. We have observed disease-dependent differentially expressed genes, including C1R, C1S, SERPING1, C4A/B, and differentially expressed cellular pathways within the DG, including cell migration, apoptosis, and neurogenesis.

Conclusions: HS and no-HS diagnosis groups have distinct DG morphometry and gene expression profile.